

Long-Term Survival Among Patients With Hodgkin's Lymphoma Who Developed Breast Cancer: A Population-Based Study

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ABSTRACT

Purpose

The increased risk of breast cancer (BC) among women receiving chest radiotherapy for Hodgkin's lymphoma (HL) is well-established. However, there are no large population-based studies that describe overall survival (OS) and cause-specific survival (CSS) compared with women with first primary BC.

Methods

For 298 HL survivors who developed BC (HL-BC group) and 405,223 women with a first or only BC (BC-1 group), actuarial OS and CSS were compared, accounting for age, BC stage, hormone receptor status, sociodemographic status, radiation for HL, and other variables. All patients were derived from the population-based Surveillance, Epidemiology, and End Results program.

Results

OS among patients with HL-BC was significantly inferior that of to patients with BC-1: 15-year OS was 48% versus 69% ($P < .0001$) for localized BC, and 33% versus 43% ($P < .0001$) for regional/distant BC. Patients with HL-BC had a significantly increased seven-fold risk ($P < .0001$) of death from other cancers (ie, not HL or BC) compared with patients with BC-1. Mortality from heart disease among patients with HL-BC with either localized or regional/distant disease was also significantly increased (hazard ratio = 2.22, $P = .04$; and hazard ratio = 4.28, $P = .02$, respectively) compared with patients with BC-1. Although 10-year BC-CSS was similar for patients with HL-BC and BC-1 with regional/distant disease, it was inferior for patients with localized BC (82% v 88%, respectively; $P = .002$).

Conclusion

Women with HL may survive a subsequent diagnosis of BC, only to experience significant excesses of death from other primary cancers and cardiac disease. Greater awareness of screening for cardiac disease and subsequent primary cancers in patients with HL-BC is warranted.

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INTRODUCTION

Hodgkin's lymphoma (HL) is a highly curable disease,¹ though the excellent life expectancy is offset by late effects of successful radiotherapy and chemotherapy, particularly the development of second malignancies.²⁻⁵ Fifteen to 30 years after therapy, cumulative mortality due to all second primary cancers exceeds deaths resulting from HL.^{3,6-8} Breast cancer (BC) accounts for the largest absolute risk of second cancers among female survivors of HL,² with increased risks documented in numerous reports.^{2,4,5,9-16} For women treated for HL at age 25 years with chest doses of ≥ 40 Gy, without alkylating agents, Travis et al¹² estimated that the cumulative

risk of BC by age 55 years is almost one in three. Despite these sobering statistics, few studies have addressed survival after BC diagnosis in women with HL.^{9,17-22} Most investigations consist of single-institution series,^{17,18,20,21} based on relatively small numbers of patients (range, 25 to 65 patients), followed-up for a median of less than 10 years.¹⁷⁻²⁰ Although several investigations analyzed patient survival by BC stage,¹⁷⁻¹⁹ no studies have simultaneously controlled for the effects of age, hormone receptor status, year of BC diagnosis, and radiotherapy for HL. The actuarial calculation of other causes of death, from either heart disease, which is known to be significantly increased after radiotherapy for HL,^{23,24} or from other cancers, has

also not been taken into account, although several reports addressed overall survival (OS),^{9,20-22} disease-free survival,^{17,20} and/or disease-specific survival.^{18,19,21}

Within a cohort of 9,948 women with a first primary HL reported to population-based cancer registries comprising the Surveillance, Epidemiology, and End Results (SEER) program, we identified patients with a new primary BC diagnosis after HL (HL-BC group). We hypothesized that OS and BC cause-specific survival (CSS) of these patients would be worse than for women in the SEER database with a first or only primary BC diagnosis (BC-1 group) and would be impacted by sociodemographic status and race. We compared OS, BC-CSS, CSS from other cancers, and heart disease CSS between groups. Patient-related, treatment-associated, and cancer-related variables were also analyzed to assess their effect on survival outcomes.

METHODS

Patient Database

From the US population-based SEER 9 (1973 to 2006) limited-use database,²⁵ 317 HL survivors were registered with an incident new primary BC. Fourteen were not actively followed-up by the SEER program, and in five others, BC stage was unavailable; the remaining 298 patients were included in our analyses. For the BC-1 comparison group, 405,223 women were analyzed. For both groups, women with unstaged BC or ductal carcinoma in situ were excluded, as were "death certificate only," "autopsy only," and cases without active follow-up. Women who developed additional ipsilateral or contralateral BCs after initial BC diagnosis were not excluded.

Of the 298 patients with HL-BC, 18 patients developed a second cancer before developing BC, including cervix (n = 7), thyroid (n = 5), vulva (n = 1), uterus (n = 1), lip (n = 1), lung (n = 1), bladder (n = 1), and non-Hodgkin's lymphoma (NHL, n = 1). At last follow-up, 12 of these 18 patients were alive, and six had died: three as a result of BC, one as a result of "miscellaneous cancer," one as a result of "other cause of death," and one as a result of sepsis.

HL stage was determined from SEER extent of disease fields (see Appendix, online only). BC was staged using the "SEER historic stage A" variable, categorized as limited (ie, confined to breast tissue, excluding T4 tumors), regional (ie, lymph node involvement and/or locally advanced tumors), or distant (ie, metastatic). Information about radiation fields, radiation dose, chemotherapy, or hormonal therapy is not available in the SEER database, though radiotherapy for HL usually includes thoracic radiation.

Statistical Analysis

Actuarial OS and CSS were calculated using the Kaplan-Meier method. "Any other cancer" CSS reflects death from any cancer other than BC or HL. Survival times were measured from date of BC diagnosis until date of death or last follow-up. For the BC-1 group, actuarial survival was calculated for randomly selected subsets of patients, matched to the HL-BC group for sociodemographic status, age, and year of BC diagnosis (described in the Appendix, online only). Cox regression was used to compare survival outcomes, controlling for covariates. All analyses were conducted using SAS 9.1.3 software (SAS Institute, Cary, NC). Kaplan-Meier curves were prepared using R 2.7.0.²⁶

RESULTS

Patient and Tumor Characteristics

Patient and tumor characteristics at time of HL diagnosis, grouped by stage of subsequent BC, are outlined in Table 1. Seventy-three percent of patients received HL treatment before age 40 years, the time of greatest radiocarcinogenicity of the breast.^{16,27} Eighty percent of women younger than 40 years and 73% of all women

Table 1. Patient and Tumor Characteristics at Time of HL Diagnosis Among 298 Women Who Developed a Second Primary Breast Cancer

Characteristic	Second Primary Breast Cancer								P*
	All		Localized		Regional		Distant		
	No.	%	No.	%	No.	%	No.	%	
Total No. of patients	298†		187		90		21		
Age at HL diagnosis, years									.016
< 10-19	66	22	33	18	28	31	5	24	
20-39	152	51	96	51	46	51	10	48	
40-59	48	16	34	18	10	11	4	19	
≥ 60	32	11	24	13	6	7	2	10	
Race									.36
White	270	91	173	93	80	89	17	81	
Black	24	8	12	6	9	10	3	14	
Other	4	1	2	1	1	1	1	5	
Year of HL diagnosis									.06
1973-1979	100	34	67	36	30	33	3	14	
1980-1989	145	49	87	47	48	53	10	48	
1990-1999	49	16	32	17	20	22	7	33	
2000-2006	4	1	1	1	2	2	1	5	
Subtype of HL									.35
Nodular sclerosis	213	71	132	71	64	71	17	81	
Mixed cellularity	43	14	32	17	8	9	3	14	
Lymphocyte depleted	7	2	4	2	2	2	1	5	
Nodular lymphocyte predominant or lymphocyte rich	10	3	7	4	3	3	0		
Classic, NOS	25	8	12	6	13	14	0		
Stage of HL‡									.50
I	85	29	56	30	23	26	6	29	
II	104	35	64	34	36	40	5	24	
III-IV	94	31	57	30	27	30	10	48	
Unknown	14	5	10	5	4	4	0		
Radiotherapy for HL									.74
Yes	217	73	136	73	67	74	14	67	
No	75	25	46	25	22	24	7	33	
Unknown	6	2	5	3	1	1	0		

Abbreviations: HL, Hodgkin's lymphoma; NOS, not otherwise specified.

*P values represent χ^2 test comparing distribution of the specific variables between the localized, regional, and distant groups.

†For an additional five HL survivors who developed breast cancer, stage was not provided in the Surveillance, Epidemiology, and End Results database.

‡Refer to the online-only Appendix for an explanation of the assignment of HL stage. In women assigned more than one possible HL stage, the higher stage is depicted in this table.

received radiation for HL. More than 80% were diagnosed with HL before 1990.

Table 2 outlines clinicopathologic features of patients with HL-BC and BC-1 at time of BC diagnosis. For patients with HL-BC, 187 (63%), 90 (30%), and 21 (7%) had localized, regional, and distant BC, respectively, with comparable percentages (60%, 34%, and 6%, respectively) for first primary BCs. Among women with HL-BC, 67% diagnosed before 1996 had localized disease versus 61% diagnosed from 1996 to 2006 ($P = .33$). Because only 21 patients with HL-BC had distant disease (Table 1), regional and distant subgroups were combined for subsequent analyses. Median latency between diagnoses of HL and BC was 15.2 years (range, 0.6 to 33.3 years) and 15.3 years (range, 0.3 to 32.0 years), respectively, for localized and regional/distant BC. Patients with HL-BC were significantly ($P < .0002$)

Table 2. Patient and Tumor Characteristics at Time of Breast Cancer Diagnosis for Women With HL-BC and Women With BC-1

Characteristic	Localized				Regional and Distant			
	HL-BC		BC-1		HL-BC		BC-1	
	No.	%	No.	%	No.	%	No.	%
Total No. of patients	187	63	241,128	60	111	37	164,095	40
Age at breast cancer diagnosis, years								
≤ 39	48	26	14,028	6	45	41	13,558	8
40-59	96	51	93,239	39	53	48	70,556	43
60-69	22	12	56,602	23	8	7	36,185	22
≥ 70	21	11	77,259	32	5	5	43,796	27
P			< .0001				< .0001	
Race*								
Black	12	6	16,363	7	12	11	15,983	10
White	173	93	209,351	87	97	87	138,778	85
Other	2	1	14,790	6	2	2	9,005	6
Unknown	0		624	< 1	0		329	< 1
P†			.04				.4	
P‡			> .6				> .8	
Latency from HL to breast cancer, years								
0 to 5	16	9	NA		9	8	NA	
> 5 to 10	35	19	NA		17	15	NA	
> 10 to 15	42	22	NA		28	25	NA	
> 15 to 20	49	26	NA		32	29	NA	
> 20 to 25	31	17	NA		17	15	NA	
> 25	14	7	NA		8	7	NA	
Year of breast cancer diagnosis								
1973-1979	0		25,504	11	2	2	26,265	16
1980-1989	21	11	58,243	24	11	10	48,216	29
1990-1999	81	43	90,212	37	37	33	49,720	30
2000-2006	85	45	67,169	28	61	55	39,894	24
P§			< .0001				< .0001	
Sociodemographic status*								
Group 1 (highest)	82	44	64,407	27	43	39	36,350	22
Group 2	64	34	61,978	26	39	35	36,311	22
Group 3	29	16	58,595	24	20	18	40,869	25
Group 4 (lowest)	11	6	48,675	20	8	7	46,249	28
Indeterminate	1	1	7,473	3	1	1	4,316	3
P			< .0001				< .0001	
Breast cancer grade								
Well differentiated	24	13	34,324	14	6	5	7992	5
Moderately differentiated	51	27	64,837	27	28	25	35,537	22
Poorly differentiated	62	33	48,556	20	54	49	47,116	29
Undifferentiated; anaplastic	4	2	4,560	2	2	2	4,618	3
Unknown	46	25	88,851	37	21	19	68,832	42
P†			.02				> .2	
Estrogen receptor status								
Positive	87	47	105,641	44	48	43	56,296	34
Borderline positive	0		803	< 1	0		574	< 1
Negative	50	27	27,828	12	35	32	20,248	12
Unavailable or unknown	50	27	106,856	44	28	25	86,977	53
P†			< .0001				.004	
Progesterone receptor status								
Positive	77	41	90,508	38	42	38	47,915	29
Borderline positive	3	2	1,245	< 1	0		757	< 1
Negative	57	30	40,299	17	39	35	27,426	17
Unavailable or unknown	50	27	109,076	45	30	27	87,997	54
P†			.005				.06	
Surgery for breast cancer								
Primary resection	184	98	237,473	98	100	90	148,411	90
Partial mastectomy	57	30	107,803	45	13	12	34,832	21
Mastectomy	124	66	91,385	38	83	75	77,118	47
Resection or mastectomy NOS	3	2	38,285	16	4	4	36,461	22
None	3	2	3,637	2	11	10	15,653	10
Unknown or not available	0		18	< 1	0		31	< 1
P†			< .0001				< .0001	

(continued on following page)

Table 2. Patient and Tumor Characteristics at Time of Breast Cancer Diagnosis for Women With HL-BC and Women With BC-1 (continued)

Characteristic	Localized				Regional and Distant			
	HL-BC		BC-1		HL-BC		BC-1	
	No.	%	No.	%	No.	%	No.	%
Radiation for breast cancer								
Radiation delivered	36	19	91,493	38	16	14	61,696	38
External beam	33		87,971		15		60,173	
Radioactive implants	3		960		0		120	
Combination beam + implants	0		1,731		1		774	
Radiation NOS	0		831		0		629	
None	146	78	144,755	60	92	83	96,725	59
Refused	0		1,442	< 1	0		1,051	1
Unknown	5	3	3,438	1	3	3	4,623	3
<i>P</i> †	< .0001				< .0001			

NOTE. *P* values represent χ^2 test comparing the distribution between HL-BC and BC-1 patients for the indicated variable.

Abbreviations: HL-BC, breast cancer after Hodgkin's lymphoma; BC-1, first or only primary breast cancer; NA, not applicable; NOS, not otherwise specified.

*At the time of breast cancer diagnosis for each patient, the proportion of adults age ≥ 25 years within the same county of residence with less than a high-school education was determined from census data, as a surrogate for sociodemographic status.²⁸ The table depicts quartiles of sociodemographic status. For those patients with missing information, sociodemographic status is considered indeterminate.

†Represents χ^2 test omitting patients with unknown or unavailable variables.

‡Represents χ^2 test comparing only the distribution of black and white patients between the HL-BC v BC-1 groups. The significant difference ($P = .04$) in the first χ^2 test reflects a greater percentage of patients with other race (American Indian/Alaska Native, Asian/Pacific Islander) in the BC-1 group.

§Refer to text. The more recent calendar year intervals of breast cancer diagnosis observed for the HL-BC patients is expected, given that Hodgkin's lymphoma diagnosed before 1973 would not have been reported to the SEER registries, in conjunction with the latency period of about 10 years for the development of radiation-induced breast cancer.

younger than patients with BC-1 (median age, 45 and 61 years, respectively) and had a higher sociodemographic status (defined in Table 2).²⁸ Only 28 patients with HL-BC were nonwhite, consistent with the more common occurrence of HL in whites. Exclusion of these patients from subsequent analyses did not impact results. A greater proportion of BC-1 patients had unknown tumor grade, and unknown estrogen receptor (ER) and progesterone receptor (PR) status. The latter finding reflects the fact that most (89%) patients with HL-BC were diagnosed after 1990, when SEER registries initiated collection of ER and PR data. Among patients with BC for whom hormonal status was reported, those with antecedent HL were significantly more likely to have ER-negative and PR-negative BC. Among patients with localized BC for whom grade was reported, those with antecedent HL were more likely to have poorly differentiated cancer ($P = .02$).

There was no significant difference in tumor size distribution between patients with HL-BC and BC-1 with localized disease (data not shown). For localized BC, patients in the HL-BC group were more likely to have undergone a complete mastectomy than those in the BC-1 group (66% v 38%; $P < .0001$) and less likely to have undergone radiotherapy (19% v 38%; $P < .0001$). Similar findings were observed among patients with HL-BC with regional/distant BC. Among patients with HL-BC having localized BC, 35% who underwent partial mastectomy did not receive breast radiation (70% of these patients had received prior radiation for HL), as compared with 22% of patients with BC-1 ($P = .015$).

Vital Status at Last Follow-Up and Cause of Death

Table 3 outlines vital status at last follow-up and causes of death. Of patients with HL-BC, 55%, 28%, 10%, and 7% were followed up less than 5, 5 to 9, 10 to 14, and ≥ 15 years after BC diagnosis. Comparable numbers in the BC-1 cohort were 40%, 26%, 16%, and 19%, respectively. Of patients with HL-BC, 109 (37%) were deceased, compared with 187,308 (46%) of patients with BC-1. Of 58 women

with HL-BC having localized BC who died, comparable percentages died from BC (38%) and other cancers (34%), whereas no deaths were attributed to HL. Not surprisingly, of 51 deaths among women with HL-BC having regional/distant BC, most resulted from BC (59%), similar to 64% of deaths in the BC-1 group.

For 28 patients with HL-BC who died of other cancers, median latency from HL to BC was 12.6 years (range, 0.6 to 27 years). Twenty-two had received radiation for HL, diagnosed at age 13 to 75 years (median, 29 years). Causes of death were lung cancer ($n = 8$), NHL ($n = 7$), esophageal cancer ($n = 1$), colon cancer ($n = 1$), anal cancer ($n = 1$), sarcoma ($n = 1$), and "miscellaneous malignant cancer" ($n = 9$). Among the seven patients whose death was attributed to NHL, five patients died ≥ 5 years after HL diagnosis (≥ 10 years in four patients). Among the nine patients dying from miscellaneous malignant cancer, four patients had third primary cancers reported to the SEER program (metastatic carcinoid, metastatic lung cancer, sarcoma, and malignant meningioma) that could have accounted for their deaths. Among the 19 other patients for whom a specific cancer death was reported, 11 patients had a separate SEER case listing that matched the cause of death, whereas eight patients did not. Among these 11 patients, the median latency from diagnosis of HL to the third primary cancer was 18 years (range, 5.2 to 31 years). Subsequent survival for these 11 patients was poor (median, 7 months; range, 2 months to 5.2 years).

Eight patients with HL-BC (10% of 83 cancer-related deaths) and 4,595 patients with BC-1 (4% of 106,208 cancer-related deaths) died as a result of lung/bronchial cancer; nine patients with HL-BC (11% of 83 cancer-related deaths) and 2,992 patients in the BC-1 group (3% of 106,208 cancer-related deaths) died as a result of miscellaneous malignant cancers. These differences between the HL-BC and BC-1 groups in the rates of deaths from lung/bronchial

Table 3. Vital Status at Last Follow-Up and Cause of Death: Women With HL-BC (n = 298) and Women With BC-1 (n = 405,223)

Vital Status	Localized				Regional				Distant				Regional/Distant			
	HL-BC		BC-1		HL-BC		BC-1		HL-BC		BC-1		HL-BC		BC-1	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Alive	129	69	151,892	63	54	60	62,246	45	6	29	3,777	15	60	54	66,023	40
Deceased	58	31	89,236	37	36	40	75,918	55	15	71	22,154	85	51	46	98,072	60
Cause of death*																
Breast cancer	22†	38	24,989†	28	20	56	44,670	59	10	67	18,234	82	30	59	62,904	64
Hodgkin's lymphoma	0		18	< 1	2	6	10	< 1	1	7	0		3	6	10	< 1
Other cancer‡	20	34	11,292	13	5	14	5,777	8	3	20	1,218	5	8	16	6,995	7
Heart disease	8	14	20,957	23	3	8	10,443	14	0		1,053	5	3	6	11,496	12
Other causes§	8	14	31,980	36	6	17	15,018	20	1	7	1,649	7	7	14	16,667	17
All	187		24,1128		90		138,164		21		25,931		111		164,095	

Abbreviations: HL-BC, breast cancer after Hodgkin's lymphoma; BC-1, first or only primary breast cancer.

*Percentages for cause of death represent percentage of all deaths.

†For women with localized breast cancer who died as a result of breast cancer, 4 (18%) of 22 HL-BC patients were registered in the Surveillance, Epidemiology, and End Results program as developing an incident contralateral breast cancer v 1,956 (8%) of 24,989 of BC-1 patients ($P = .071$).

‡Other cancer causes of death included lung (n = 8), esophagus (n = 1), colon (n = 1), anal (n = 1), non-Hodgkin's lymphoma (n = 5), sarcoma (n = 1), and miscellaneous cancer (n = 3) among women with localized breast cancer and non-Hodgkin's lymphoma (n = 2) and miscellaneous cancer (n = 6) among women with regional/distant breast cancer.

§For women with localized breast cancer, other causes included chronic liver disease (n = 1), chronic obstructive lung disease (n = 1), pneumonia or influenza (n = 1), other causes (not specified, n = 3), and not available (n = 2). For women with regional/distant breast cancer, other causes included chronic liver disease (n = 1), hypertension without heart disease (n = 1), ill-defined condition (n = 1), infectious disease or sepsis (n = 2), and other causes (not specified, n = 2).

cancer and miscellaneous cancers are consistent with the known increased risk of solid tumors among HL survivors (see Discussion).

Survival of HL-BC Versus BC-1 Groups

Table 4 and Figures 1A through 1C summarize the actuarial OS, BC-CSS, and other cancer CSS probabilities of patients with HL-BC and BC-1, matched for age, year of BC diagnosis, and sociodemographic status. Table 4 shows P values and hazard ratios (HRs) derived from Cox models comparing survival. Adjusting for covariates, the HL-BC group had a significantly poorer OS. Patients in the HL-BC group having localized disease had a significantly two-fold increased mortality ($P < .0001$) from either BC or heart disease as compared with patients in the BC-1 group. Patients in the HL-BC group with regional/distant disease demonstrated a significantly increased four-fold relative mortality from heart disease, with a nonsignificant 30% excess risk of death resulting from BC. It is noteworthy that HL survivors with localized or regional/distant BC had approximately seven times the hazard of death from other cancers as compared with patients with BC-1. Patients with regional/distant disease had a 4.7-fold increased risk of death from causes other than cancer or heart disease (refer to Table 3 footnote).

Prognostic Factors Among HL Survivors With BC

Table 5 shows results of univariate and multivariate analyses of prognostic factors that could potentially impact OS or BC-CSS in patients with HL-BC. For OS, age at BC diagnosis was inversely related to survival ($P = .0003$ and $P = .004$, respectively, for women with either localized or regional/distant BC). ER negativity was an adverse prognostic factor for OS among women with distant/regional BC. For women with localized BC, lower sociodemographic status was an adverse predictor ($P = .04$) of BC-CSS. For women with regional/distant BC, radiation for HL (HR = 2.61; $P = .03$) and ER negativity (HR = 3.07; $P = .02$) were significant adverse risk factors for BC-CSS.

No other tested variable was a statistically significant predictor for OS or CSS in the multivariate analyses.

DISCUSSION

An important new finding in our study, based on 298 patients with HL-BC and 405,223 patients with BC-1, is the observation that HL survivors in the general population who develop BC, as compared with women with a first or only BC, are at a significantly increased seven-fold risk of death from other cancers. Moreover, these patients experience significantly elevated two- to four-fold greater risks of cardiac death. For the first time, to our knowledge, the OS and CSS beyond 10 years, as well as the influence of several clinicopathologic factors (ie, sociodemographic status) on survival outcomes, are evaluated among patients with HL who develop BC. We show that lower sociodemographic status adversely affects both BC-CSS ($P = .04$) and OS ($P = .09$) among women who develop localized BC after HL.

Whereas the increased risk of new primary cancers in patients with HL is well-established,^{2,6,7,22,29} few studies address the development of two or more cancers after HL² or subsequent mortality due to these malignancies.^{6,7} To our knowledge, none have addressed cancer mortality among HL survivors who develop BC. In our study, deaths from third or high-order cancers occurred at sites for which significantly increased risks of second cancers have been reported,^{2,4,22,29-31} including NHL,^{2,4,5,22,31,32} cancers of lung,^{2,4,22,29,31,33} esophagus,^{2,4,30,31} colon,^{2,4,22,30,31} anus,³⁰ soft tissue,^{2,4,30,31} and brain.^{2,30}

HL survivors have a significantly increased three- to 10-fold risk of lung cancer,^{2,4,22,29,31,33} with associated risk factors including prior radiation, alkylating-agent chemotherapy (both with significant dose-responses), and smoking history.^{33,34} Virtually all lung cancers develop in HL survivors who smoke.^{33,34} Thoracic radiation and smoking history also significantly increase the risk of lung cancer after BC.^{35,36} Although it is possible that deaths resulting from metastatic

Survival of Patients With Hodgkin's Lymphoma Who Develop Breast Cancer

Table 4. Comparison of Actuarial Survival Probabilities: Women With HL-BC (n = 298) Versus Women With BC-1 (n = 405,223)

Survival Category	Localized		Regional/Distant	
	HL-BC	BC-1	HL-BC	BC-1
Overall survival				
5-year OS, %	77	89	55	67
10-year OS, %	59	72	38	52
15-year OS, %	48	58	33	42
<i>P</i> (Cox model: multivariate)*	< .0001		< .0001	
Cox multivariate HR†	2.82		2.22	
95% CI	2.17 to 3.67		1.68 to 2.93	
Breast cancer CSS				
5-year CSS, %	91	92	68	72
10-year CSS, %	82	85	58	59
<i>P</i> (Cox model: multivariate)*	.002		.15	
Cox multivariate HR†	2.01‡		1.31	
95% CI	1.31 to 3.08		0.91 to 1.89	
Any other cancer CSS				
5-year CSS, %	92	99.6	93	98
10-year CSS, %	84	97	86	97
<i>P</i> (Cox model: multivariate)*	< .0001		< .0001	
Cox multivariate HR†	7.03		6.87	
95% CI	4.53 to 10.91		3.43 to 13.75	
Heart disease CSS				
5-year CSS, %	96	99	97	99
10-year CSS, %	93	96	92	98
<i>P</i> (Cox model: multivariate)*	.04		.02	
Cox multivariate HR†	2.22		4.28	
95% CI	1.06 to 4.65		1.38 to 13.27	
Any other disease CSS				
5-year CSS, %	97	98	93	98
10-year CSS, %	91	94	87	96
<i>P</i> (Cox model: multivariate)*	.31		< .0001	
Cox multivariate HR†	1.43		4.71	
95% CI	0.72 to 2.86		2.24 to 9.88	

NOTE. The 5-, 10-, and 15-year actuarial survival outcomes of the BC-1 group represent survival of randomly selected subsets of patients matched to the HL-BC group for age at breast cancer diagnosis, year of breast cancer diagnosis, and sociodemographic status as described in the online-only Appendix. For localized BC, 3,927 BC-1 patients were randomly selected from within strata matched to the 187 HL-BC patients; for regional/distant BC, 4,329 BC-1 patients were randomly selected from within strata matched to the 111 HL-BC patients. These matching analyses were repeated 100 times, and the calculated Kaplan-Meier actuarial survival of the BC-1 group represent an average of 100 matched survival curves.

Abbreviations: HL-BC, breast cancer after Hodgkin's lymphoma; BC-1, first or only primary breast cancer; OS, overall survival; HR, hazard ratio; CSS, cause-specific survival.

*These *P* values (*P* value Cox model: multivariate) reflect the statistical significance of survival differences, calculated from a Cox model that includes age at breast cancer diagnosis, Hodgkin's lymphoma status, calendar year of breast cancer diagnosis, estrogen receptor status, progesterone receptor status, radiotherapy for breast cancer, sociodemographic status at time of breast cancer diagnosis, and race. As this model primarily reflects risk factors among the BC-1 population (which exceeds the HL-BC patients by > 1,000-fold), the *P* values of these other variables are not shown. The interested reader is referred to Appendix Tables A1 and A2, online only.

†The HR reflects risk of death of HL-BC as compared with BC-1 patients, using a Cox model incorporating age at breast cancer diagnosis, Hodgkin's lymphoma status, calendar year of breast cancer diagnosis, estrogen receptor status, progesterone receptor status, radiotherapy for breast cancer, sociodemographic status at time of breast cancer diagnosis, and race.

‡To determine the impact of contralateral breast cancer, we treated the incidence of a contralateral breast cancer as a censoring event, just like another cause of death. There were four HL-BC patients and 1,956 BC-1 patients with localized disease who developed a contralateral breast cancer. Censoring them yielded an HR for BC-CSS of 1.73 (95% CI, 1.71 to 2.78; *P* = .024), which is only slightly less than the uncensored results (HR = 2.01). Thus contralateral breast cancer can only explain a small part of the worse BC-CSS of HL-BC patients with localized breast cancer.

BC were erroneously ascribed to lung cancer for either patients with HL-BC or BC-1, the reported rate of such misclassification is low.³⁷ Without independent histopathologic review, unequivocal classification of incident lung cancer after BC is not possible.

HL survivors have a significantly increased five-fold to more than 20-fold risks of NHL, with excesses persisting for more than 15 years after HL.^{2,4,5,22,31,32} Although death attributed to NHL in our study could have represented misclassified HL, this type of error is less likely in patients with a lengthy interval between the two lymphoma diagnoses. Similarly, although women originally assigned a diagnosis of

HL could have actually had NHL, this type of misclassification occurs in only approximately 2% of patients.³²

Using an actuarial comparison, patients in the HL-BC group had a significantly increased two- to four-fold risk of death from heart disease as compared with patients in the BC-1 group. Although patients with either HL²³ or BC³⁸ are susceptible to treatment-related cardiac toxicities (attributable to radiation and/or anthracycline chemotherapy), HL survivors tend to receive these exposures at a considerably younger age. Moreover, compared with patients with BC, patients with HL are generally

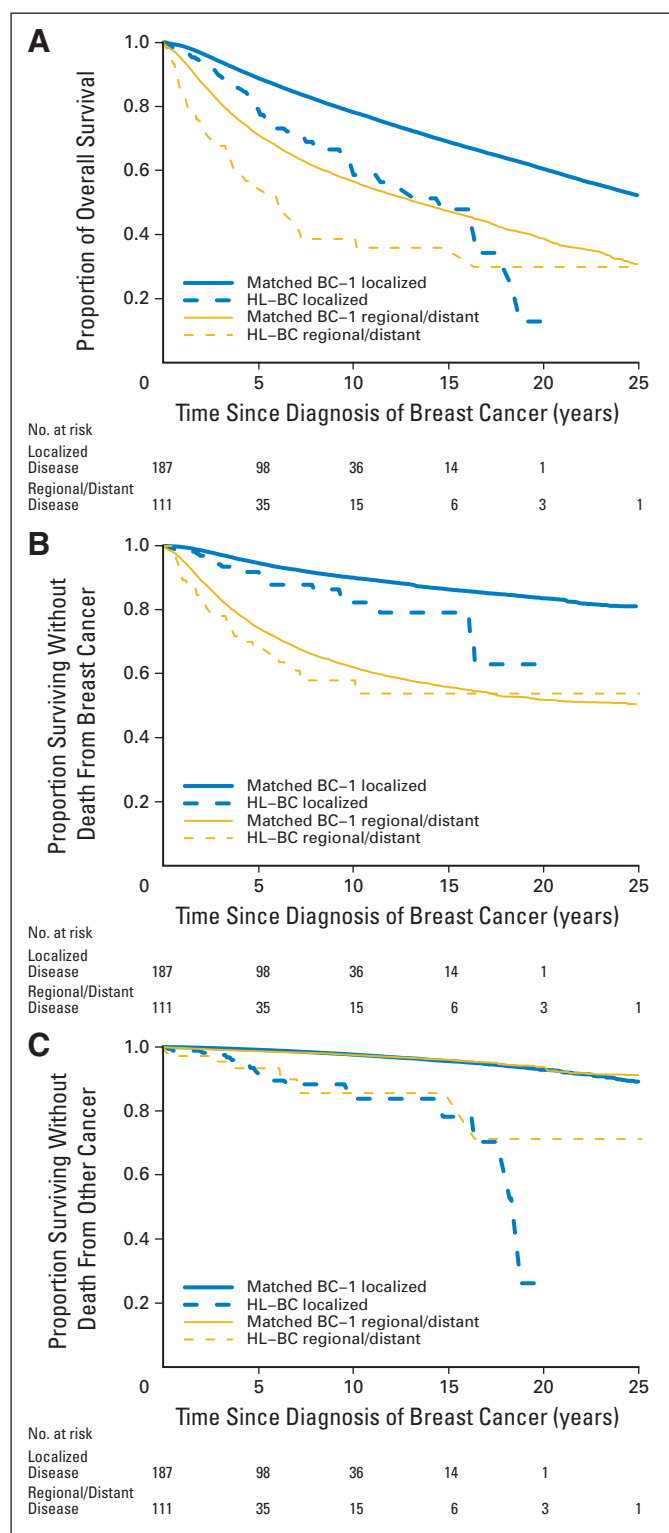


Fig 1. Comparison of (A) overall survival, (B) survival without death from breast cancer, and (C) survival without death from any other cancer (ie, excluding Hodgkin's lymphoma [HL] and breast cancer) for women with first primary breast cancer (BC-1, solid lines) and those with breast cancer after HL (HL-BC, dashed lines). For the BC-1 group, actuarial survival was calculated for a subset and matched to the HL-BC group for sociodemographic status, age, and year of BC diagnosis (described in online-only Appendix and Table 4 footnotes). Estimates for localized breast cancer (BC-1 and HL-BC) are shown in blue, whereas those for regional/distant disease (BC-1 and HL-BC) are shown in gold. Number at risk indicates the number of patients with HL with new primary breast cancer at risk at the indicated time interval.

Table 5. Variables That Affect Outcome in Women With HL Who Develop BC

Variable	Localized		Regional/Distant	
	Overall Survival	BC Cause-Specific Survival	Overall Survival	BC Cause-Specific Survival
Univariate analysis, <i>P</i>				
HL stage*	.89-.99	.74-.90	.42-.94	.51-.80
Radiation for HL	.62	.45	.30	.04
Latency of BC†	.48	.88	.22	.24
Age at BC diagnosis‡	< .001	.19	.005	.52
Year of BC diagnosis‡	.10	.40	.90	.27
Sociodemographic status‡	.02	.06	.63	.28
ER status‡	.42	.45	.16	.02
ER status§	.86	.42	.06	.02
PR status‡	.88	.38	.15	.04
PR status§	0.66	.87	.06	.04
Multivariate analysis				
Radiation for HL	ND	ND	ND	
<i>P</i>				.03
HR				2.61
Age at BC diagnosis				ND
<i>P</i>	.0003	.14	.004	
HR	1.04	0.980	1.03	
Year of BC diagnosis		ND	ND	ND
<i>P</i>	.96			
HR	1.00			
Sociodemographic status			ND	ND
<i>P</i>	.09	.04		
HR	1.05	1.08		
ER negative	ND	ND		
<i>P</i>			.05	.02
HR			2.06	3.07

NOTE. Variables with *P* values < .2 in the univariate analyses were entered into the multivariate analysis. PR status was not entered into the multivariate model because of the small sample size and high correlation between ER status and PR status.

Abbreviations: HL, Hodgkin's lymphoma; BC, breast cancer; ER, estrogen receptor; PR, progesterone receptor; ND, not done, because *P* value was > 0.2 with univariate analysis; HR, hazard ratio.

*As described in the online-only Appendix, HL stage was assigned in four different ways. The influence of stage was not statistically significant when the influence of stage was tested using any of these schema. The range of *P* values is shown in the table.

†These variables were analyzed with a Cox model using the single variable of interest; all others were analyzed using the log-rank method.

‡Log-rank test which reflects difference in survival between patients according to hormone receptor status (ie, positive v negative v borderline v unknown).

§These analyses excluded patients for whom receptor status was either borderline or unknown.

given higher anthracycline doses and are irradiated to larger cardiac volumes, albeit at lower doses.³⁹ The higher risk of cardiac death after HL is also noteworthy in view of the common use of mechlorethamine, vincristine, procarbazine, and prednisone chemotherapy during much of the study period (1970s to mid 1980s), after which doxorubicin, bleomycin, vinblastine, and dacarbazine (which includes cardiotoxic doxorubicin) became more widely used.⁴⁰

Among women with localized BC, patients in the HL-BC group had a significantly increased two-fold risk of death resulting from BC as compared with patients in the BC-1 group, which may in part be

due to an approximately two-fold (albeit nonsignificant) greater prevalence of contralateral BC (Table 3). However, contralateral BC explains only a small part of the inferior BC-CSS (Table 4), which may also reflect patient susceptibility or treatment-induced factors and/or limitations in treatment options for BC after HL. For example, HL survivors are less likely to receive anthracycline chemotherapy for BC.²¹ Moreover, our study and another investigation²¹ also showed that HL survivors are significantly less likely to receive breast-conserving surgery or radiotherapy for BC than patients with BC-1. We also found that HL survivors who underwent breast-conserving surgery were less likely to receive radiation, most likely due to prior chest radiation for HL.

BC after treatment for HL may also exhibit a different biology compared with de novo BC. In an analytic population-based study of BC after radiation for HL, archived paraffin-embedded tissues from 19 women were compared with de novo BC.⁴¹ BC after HL was characterized by a 4.2-fold increase ($P = .16$) in microsatellite alterations, reflecting widespread genomic instability.⁴¹ Moreover, loss of heterozygosity in several chromosomes were significantly greater among HL survivors versus those with de novo BC.⁴¹ In another series, BC after HL, as compared with de novo BC, had a gene expression profile characterized by high proliferation, more aggressive tumor type (in approximately 80% of HL survivors),⁴² and greater likelihood of chromosomal aberrations (unpublished work discussed in Broeks et al⁴²). Another investigation showed no differences in germ-line mutations in the ataxia-telangiectasia gene between BC after HL and de novo BC.⁴³

Because of the long follow-up in our study, we are able to report for the first time 15-year OS of HL survivors who develop BC. Two matched-pair analyses have also compared OS of HL survivors against women with a first or only BC,^{20,21} although with far fewer patients and less follow-up than in our study. One series analyzed 21 HL survivors and another evaluated 53 patients (of whom 35 patients had HL). In neither study was OS significantly different between HL survivors and those with de novo BC at time points of 5 to 10 years.^{20,21}

Compared with women with first or only BC, HL survivors were relatively younger at time of BC diagnosis; diagnosed in relatively later decades, in part reflecting the typical latency period of ≥ 10 years required for radiation-associated solid tumors²⁷; and had a higher sociodemographic status, which is known to be correlated with HL.^{44,45} BCs among HL survivors were significantly more likely to be characterized by pathologic features of poorer grade, ER negativity, and PR negativity. Whether the greater risk of ER- and PR-negative tumors in our study may somehow reflect chemotherapy-induced (specifically mechlorethamine, vincristine, procarbazine, and pred-

nison) ovarian ablation^{46,47} is not known. Yahalom et al¹⁷ compared the histologic features of 45 BCs in 37 patients previously treated for HL with those in 935 patients with first BC. Nuclear grade, histologic grade, lymphocytic reaction, and lymphatic invasion were similar between the two groups.

The primary strength of the current study is the large number of patients ($> 400,000$) including 298 with BC after HL. All patients were derived from population-based registries, with no selection biases and with long-term follow-up, strengthening the generalizability of our results. Weaknesses of the SEER database include lack of information about radiation dose and fields as well as whether or not patients received chemotherapy (or what agents they received), factors important in predicting BC risks in patients with HL.^{5,9,12,16} In addition, it should be recognized that even the initial course of radiotherapy is underreported in the SEER program.⁴⁸ With respect to BC-CSS, the power to detect covariate effects was limited because only 52 patients with HL-BC died as a result of BC, the most common cause of death in these patients. There were also small numbers of deaths from other causes.

Nonetheless, our results underscore the importance of continuing to monitor HL survivors who develop BC for late cardiac complications²³ and additional malignancies, as well as the need to counsel patients on preventive measures such as smoking cessation and healthy lifestyle modifications. Systematic lifelong follow-up is needed to examine the emergence of long-term toxicity and associated morbidity and mortality.^{49,50} Future research should be directed at examining the underlying cancer biology and etiology of treatment-induced cancers, as well as inherent and treatment-induced genetic susceptibility of HL survivors. Genetic susceptibility may not only impact risk of developing additional cancers, but also subsequent survival, and warrants careful investigation.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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